



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application

Inventors: Hoffmann, et al.

Serial No. 10/766,122, filed January 27, 2004
(Case Docket No. 21558 US)

Group: 1624
Examiner: Habte, Kahsay

For: **NEW CRYSTALLINE MODIFICATIONS OF 2-(3,5-BIS TRIFLUOROMETHYL-PHENYL)-N-[6-(1,1-DIOXO-1A⁶-THIOMORPHOLIN-4-YL)-4-(4-FLUORO-2-METHYL-PHENYL)-PYRIDIN-3-YL]-N-METHYL-ISOBUTYRAMIDE**

DECLARATION OF Olaf Grassmann, Ph.D.
UNDER 37 CFR § 1.132

Nutley, New Jersey 07110

Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Olaf Glassmann, declare that:

BACKGROUND

1. In 2003, I received a Ph.D. degree in chemistry from the University of Würzburg. In 1999, I received a diploma degree in Technical Mineralogy from Freiberg University of Mining and Technology, Freiberg, Germany.
2. A summary of my education and employment history, as well as a list of my publications, is provided in my *curriculum vitae*, a copy of which is attached hereto as Exhibit 1.

3. Since 2003, I have been employed as a Lab-Head at F. Hoffmann-La Roche Ltd, Grenzacherstrasse, CH-4070 Basel, Switzerland ("Roche"), an affiliate of the assignee of the captioned application.
4. I am familiar with the subject matter of the captioned application, filed January 27, 2004. The captioned application is directed to a new crystalline form of 2-(3,5-bis trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1 λ ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide.
5. I am familiar with the recent Patent Office Action dated January 12, 2006, in the subject application. I understand that in this Office Action, the subject application is rejected under the doctrine of obviousness-type double patenting over claims 1 to 4 of copending application no. 10/196,795, now US Patent No. 6,849,624 (hereinafter referred to as "the '624 patent"). Specifically, I understand the rejection to be that the new crystalline form of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1 λ ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide is obvious over the 2-(3,5-bis trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1 λ ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide described in the '624 patent. In particular, I understand the rejection to be that the characteristics of the new crystalline form of the instant application are inherent in the compound of claim 1 of the '624 patent.
6. I submit this declaration to show that the new crystalline form of 2-(3,5-bis trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1 λ ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide (Form A) is different from the compound disclosed in the '624 patent (Form B) and that it has different physiochemical properties that are not present in the compound of the '624 patent.

DISCUSSION

THE COMPOUND OF US PATENT 6,849,624 IS FORM B

7. It has now been found that the compound 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1 λ^6 -thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide exists in an amorphous form and in three distinct crystalline forms (Spec. ¶ [0005]). Each of the three crystalline forms can be obtained by crystallization from different types of solvents. As noted in the instant specification, Form A can be prepared by crystallization with 1-propanol, 2-propanol, or a mixture of ethanol/dichloromethane/water. (Spec. ¶¶ [0031] and [0032]) Form B can be prepared by crystallization with ethanol, acetonitrile, cyclohexane, n-hexane, methanol, methyl t-butyl ether, or water. (Spec. ¶¶ [0033] and [0034]) Form C can be prepared by incubating Form A at about 120°C in vacuum for a period of about 3 days. (Spec. ¶ [0035]) The amorphous form is prepared rapidly vacuum concentrating a solution of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1 λ^6 -thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in dichloromethane at room temperature, followed by additional drying under vacuum for about 12 hours. The amorphous form also can be prepared by fast evaporation of solutions in dioxane, ethyl acetate, isopropyl acetate, methyl ethyl ketone or tetrahydrofuran. (Spec. ¶¶ [0036] and [0037])
8. The 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1 λ^6 -thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide prepared in the '624 patent is Form B. Example 2 of the '624 patent is directed to the process for preparing 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1 λ^6 -thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide. (Col. 11, lines 51-63) This example states that the compound was prepared according to the procedure in Example 1,

which describes crystallization of the final product from ethanol. (Col. 11, lines 45-48)
As noted above, crystallization with ethanol results in Form B.

9. The compound of the '624 patent was subjected to X-ray powder diffraction using a Stoe Stadi P diffractometer equipped with a primary monochromator and a Position Sensitive Detector (PSD). Copper K-Alpha 1 radiation (1.5406\AA) was used, the generator was set to 40 KV, 50 mA. The sample was measured between 3 and 42 2θ (2θ). The resulting X-ray powder diffraction pattern is attached as Exhibit 2.

FORM A AND FORM B HAVE DIFFERENT X-RAY-DIFFRACTION PATTERNS

10. Crystalline Form A, prepared by the method of the instant application was subjected to X-ray powder diffraction as described in paragraph 9 above. The resulting X-ray powder diffraction pattern is attached as Exhibit 3.
11. As seen by the X-ray diffraction patterns in Exhibits 2 and 3, Form B is characterized by the following X-ray diffraction pattern: 8.9, 9.5, 12.3, 12.9, 15.0, 15.8, 16.2, 17.2, 17.7, 19.2, 20.4, 21.1, 22.0, and 23.9. In contrast, the claimed Form A is characterized by the following X-ray diffraction pattern: 4.5, 6.4, 7.5, 7.7, 8.0, 8.2, 10.0, 10.2, 10.9, 11.1, 12.9, 13.4, 14.0, 14.5, 15.1, 15.6, 16.2, 16.5, 17.3, 17.5, 18.0, 18.9, 19.3, 19.5, 19.9, 20.1, 20.6, 21.0, 21.4, 22.7, 23.1, and 23.6. Comparative X-ray powder diffraction patterns for forms A and B also are shown in Figure 1 of the instant application.

FORM A AND FORM B HAVE DIFFERENT INFRARED SPECTRA AND DIFFERENTIAL SCANNING CALORIMETRY

12. As shown in the specification, the Infrared Spectra for Form A and Form B also are distinct. The IR-spectra were obtained as described in Example 13. (Spec. ¶ [0072]) The results are shown in Figure 2. In particular, the IR spectra for Form A has sharp bands at 2925, 2854, 1637, 1604, 1484, 1395, 1375, 1285, 1230, 1172, 1125, 1082, 999, 943, 893, 868, 860, 782, 705, and 684 cm^{-1} . The IR spectra for Form B has sharp bands at 3051,

2924, 2854, 1655, 1599, 1542, 1494, 1467, 1397, 1364, 1327, 1275, 1229, 1177, 1158, 1128, 1081, 996, 948, 893, 826, 710, and 683 cm⁻¹.

13. Also as shown in the specification, the Differential Scanning Calorimetry (DSC) for Form A and Form B are distinct. DSC were obtained as described in Example 14. (Spec ¶¶ [0073] to [0076]). The results are shown in Figure 4. As shown, Form A has a melting point within 128.3 to 148.5°C while Form B has a melting point within 161.8 to 171.3°C.

CONCLUSION

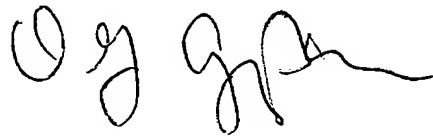
14. The data described above show that the 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide disclosed in the '624 patent is Form B. The data further show that the characteristic properties of the claimed Form A are not inherent in Form B. To the contrary, the data show that Form A and Form B have distinct physical properties, i.e. X-ray powder diffraction patterns, IR spectra, and DSC values.
15. The instant specification states that Form A has an improved pharmaceutical profile, especially for oral administration. In particular, Form A can be formulated at high concentrations. These formulations provide better substance resorption and, thus, have improved bioavailability over Form B. (Spec. ¶ [0006]) This is validated by the animal study described in Example 16 of the specification. (Spec ¶¶ [0080] to [[0092]) It is my opinion that the differences in physical properties described above contribute to the biological differences between forms A and B.
16. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Basel,

Dr. Olaf Glassmann

07.07.2006

A handwritten signature in black ink, appearing to read 'O. G. Glassmann', with a long horizontal flourish extending to the right.

235748

Exhibit 1

Dr. Olaf Grassmann

Date of birth: September, 26th 1972

Place of birth: Leverkusen, Germany

Address: Blumenmühlgasse 3
D-79400 Kandern

Citizenship: german

Profession: mineralogist

Scientific career:

1994 – 1996 Rheinische-Friedrich-Wilhelms University Bonn

1996 – 1999 Freiberg University of Mining and Technology

1999 Diploma degree in Technical Mineralogy (diploma thesis: „Herstellung biokeramischer Funktionsschichten und Schichtcharakterisierung nach Langzeitkontakt mit simulierter Körperflüssigkeit“)

2000 – 2003 University of Würzburg / Fraunhofer-Institut für Silicatforschung

2003 PhD degree in chemistry (PhD thesis “Biomimetic materials synthesis in functionalized hydrogel matrices”)

2003 - 2005 F. Hoffmann-La Roche, Basel: Lab-head X-ray Powder Diffraction

since 2006 F. Hoffmann-La Roche, Basel: Lab-head Small Molecule X-ray

Publications:

I. Sethmann, A. Putnis, O. Grassmann, P. Loebmann "Observation of nano-clustered calcite growth via a transient phase mediated by organic polyanions: A close match for biomineralization" *American Mineralogist* (2005), 90(7), 1213-1217.

O. Grassmann, P. Lobmann "Biomimetic nucleation and growth of CaCO_3 in hydrogels incorporating carboxylate groups". *Biomaterials* (2003), 25(2), 277-282.

O. Grassmann, R. Neder, A. Putnis, P. Lobmann "Biomimetic control of crystal assembly by growth in an organic hydrogel network". *American Mineralogist* (2003), 88(4), 647-652.

O. Grassmann, P. Lobmann "Morphogenetic control of calcite crystal growth in sulfonic acid based hydrogels" *Chemistry-A European Journal* (2003), 9(6), 1310-1316.

O. Grassmann, G. Mueller, P. Loebmann "Organic-Inorganic Hybrid Structure of Calcite Crystalline Assemblies Grown in a Gelatin Hydrogel Matrix: Relevance to Biomineralization" *Chemistry of Materials* (2002), 14(11), 4530-4535.

R. Heimann, O. Grassmann, T. Zumbrink, H. Jennissen "Biomimetic processes during in vitro leaching of plasma-sprayed hydroxyapatite coatings for endo-prosthetic applications" *Materialwissenschaft und Werkstofftechnik* (2001), 32(12), 913-921.

R. Heimann, O. Grassmann, M. Hempel, R. Bucher, M. Harting "Phase content, resorption resistance and residual stresses of bioceramic coatings" Editor(s): Rammlmair, Dieter. *Applied Mineralogy: In Research, Economy, Technology, Ecology and Culture*, Proceedings of the International Congress on Applied Mineralogy, 6th, Goettingen, Germany, July 17-19, 2000 (2000), 1 155-158.

O. Grassmann, R. Heimann "Compositional and microstructural changes of engineered plasma-sprayed hydroxyapatite coatings on Ti6Al4V substrates during incubation in protein-free simulated body fluid" *Journal of Biomedical Materials Research* (2000), 53(6), 685-693.

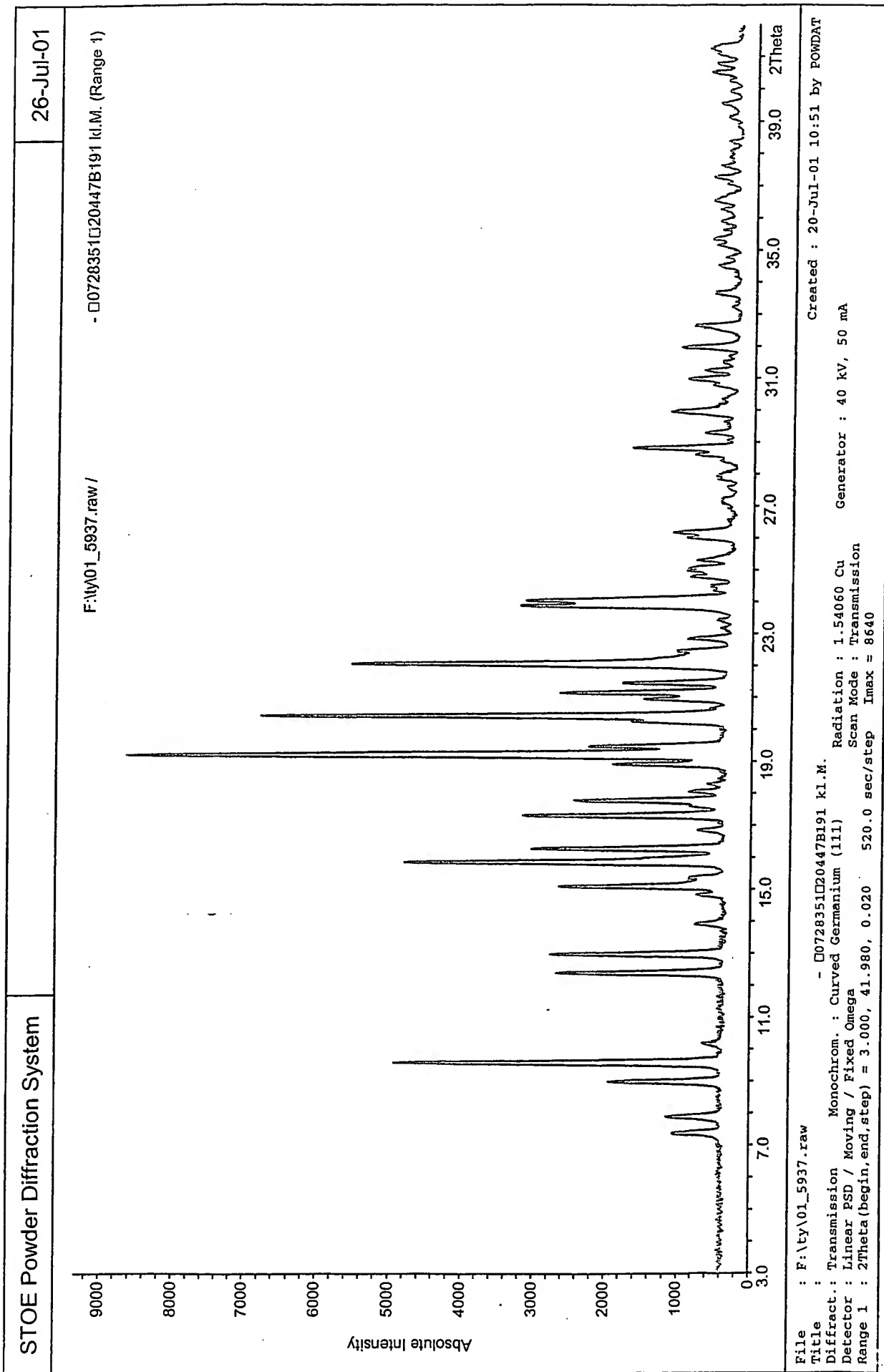
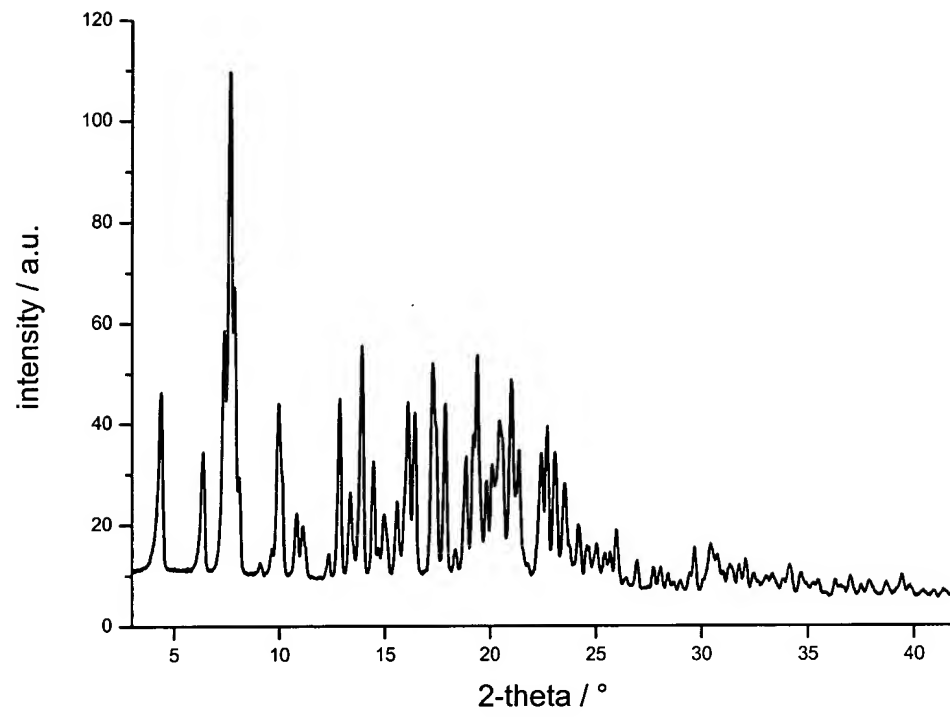


Exhibit 3



STOE Powder Diffraction System

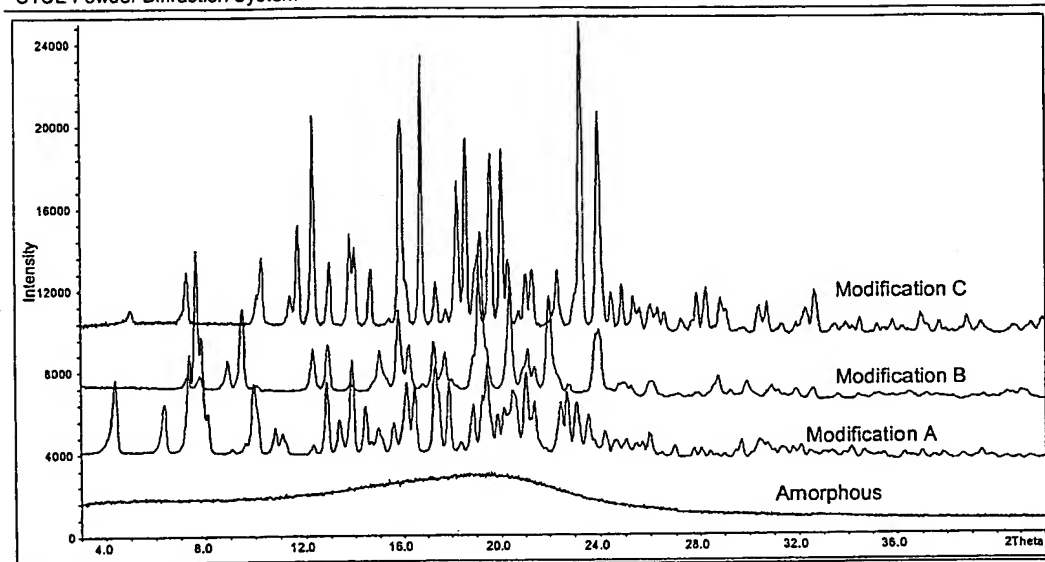


FIGURE 1

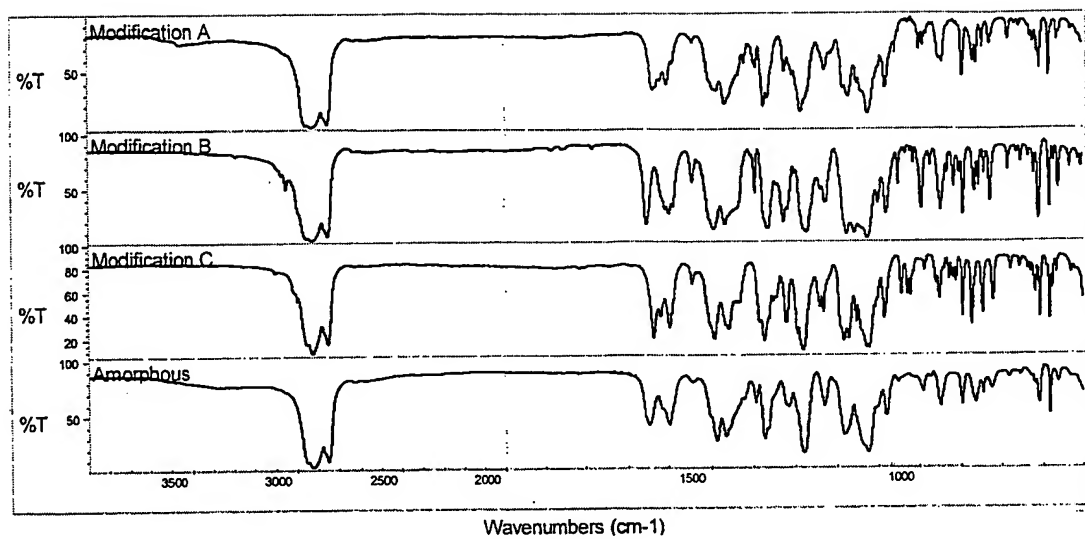


FIGURE 2

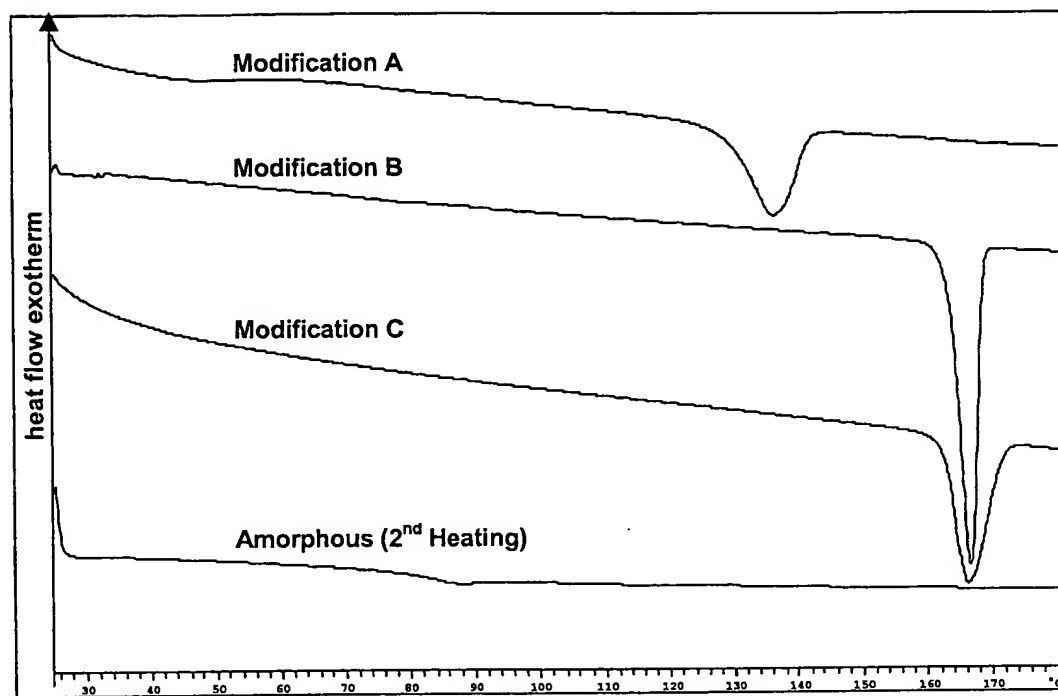


FIGURE 4